IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Appl. No.	: 09/371,354	Confirmation No. 9137
Applicant	: Donovan	
Filed	: August 10, 1999	
Title	: INTRAPERICARDIAL BOTULINUM TOXIN TREATMENT FOR BRADYCARDIA	
TC/A.U.	: 1600/1647	
Examiner	: Bunner, B.E.	
Docket No.	: D-3108	
Customer No.	: 33197	

APPELLANT'S BRIEF (37 C.F.R. 1.192)

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STATUTE

35 U.S.C. § 112. Specification.

(1) The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

(2) The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

(3) A claim may be written in independent or, if the nature of the case admits, in dependent or multiple dependent form.

(4) Subject to the following paragraph, a claim in dependent form shall contain a reference to a claim previously set forth and then specify a further limitation of the subject matter claimed. A claim in dependent form shall be construed to incorporate by reference all the limitations of the claim to which it refers.

(5) A claim in multiple dependent form shall contain a reference, in the alternative only, to more than one claim previously set forth and then specify a further limitation of the subject matter claimed. A multiple dependent claim shall not serve as a basis for any other multiple dependent claim. A multiple dependent claim shall be construed to incorporate by reference all

the limitations of the particular claim in relation to which it is being considered.

(6) An element in a claim for a combination may be expressed as a means or step for performing a specified function without the recital of structure, material, or acts in support thereof, and such claim shall be construed to cover the corresponding structure, material, or acts described in the specification and equivalents thereof.

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APPELLANT'S BRIEF

Mail Stop Appeal Brief-Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

This brief is in furtherance of a Notice of Appeal filed August 4, 2003.

I. REAL PARTY OF INTEREST

The above-identified application has been assigned to Allergan, Inc. Therefore, Allergan, Inc. is the real party of interest.

II. RELATED APPEALS AND INTERFERENCES

Neither this appeal nor the above-identified application is related to any other appeal or pending interference.

III. STATUS OF CLAIMS

Claims 1-6, 8-14, 18-36 have been cancelled. Claims 7, 15-17, and 37-38 are currently pending. Therefore, the claims on appeal

are claims 7, 15-17, and 37-38, a copy of which is included herein as Appendix A.

IV. STATUS OF AMENDMENTS

The most recent amendment was filed on February 20, 2003 in response to an Office Action dated October 18, 2002. In the amendment, claims 7 and 38 of pending claims 7, 15-17, and 37-38, were amended. Subsequently, a Final Office Action was mailed July 1, 2003 indicating that the amendment was entered in full.

No further amendment has been filed subsequent to the Final Office Action.

V. SUMMARY OF INVENTION

The present invention, as set forth in claims on appeal 7, 15-17, and 37-38, is directed to methods of treating bradycardia by administering a botulinum toxin to the sinoatrial node (SA node) or atrioventricular node (AV node) of a heart of a patient with bradycardia.

In general, and as discussed more fully herein, bradycardia is characterized by an abnormally reduced heart rate. Bradycardia may be caused, at least in part, by the release of the neurotransmitter acetylcholine from cholinergic parasympathetic neurons of the heart. A possible physiological mechanism with regard to the present invention may relate to inhibiting the acetylcholine release from cholinergic neurons of the heart by injecting a botulinum toxin in a region containing cholinergic parasympathetic neurons (i.e., the SA node or the AV node). By injecting a botulinum toxin into such a region, acetylcholine release may be attenuated. The injection resulting attenuation of acetylcholine release can lead to an increase in heart rate, thereby treating bradycardia of a patient.

VI. ISSUES

The legal issue on appeal is whether the subject matter of claims 7, 15-17, and 37-38 is sufficiently described in the specification in such a way as to enable one skilled in the art to make and or use the invention under 35 U.S.C. § 112, first paragraph.

VII. GROUPING OF CLAIMS

With respect to the grounds of rejection, the claims on appeal do not stand or fall together.

VIII. ARGUMENT

The Examiner has maintained the rejections of the claims on appeal as being unpatentable under 35 U.S.C. § 112, first paragraph because the specification allegedly does not contain a description sufficient to enable a person of ordinary skill in the art to make and use the invention. Appellant respectfully submits that the rejections are in error and submits that the present application contains a sufficient description to enable one of ordinary skill in the art to practice the claimed method.

A. Errors in the Rejection

In maintaining the rejections of the claims under 35 U.S.C. § 112, first paragraph, the Examiner has stated that the present claims are rejected because:

1. the specification does not contain any working examples of treating a patient with bradycardia by administering botulinum toxin to a patient;
2. the specification does not disclose a specific or optimal dosage of the botulinum toxin;
3. the specification does not disclose a time period for administration of a botulinum toxin to a patient;

4. the specification does not disclose side effects of administering a botulinum toxin;
5. the results of the method are complex and unpredictable when combined with the step of administering a botulinum toxin of the patient; and
6. the state of the art is contradictory.

These grounds for supporting the rejections are in error for the following reasons.

The enablement of the specification should be determined on the evidence as a whole. A declaration or affidavit is, itself, evidence that must be considered (see, e.g., MPEP § 2164.05).

In establishing and maintaining the rejections under 35 U.S.C. § 112, first paragraph, the Patent Office has essentially discounted the factual evidence presented in three declarations provided by two experts in the field of the invention, i.e., two declarations by Dr. Longhurst (an expert in the field of cardiovascular medicine, including treatment of bradycardia) and one declaration by Dr. Brin (an expert in the field of botulinum toxin therapy).

Based on an independent review of the above-identified application and in view of his individual scientific knowledge and reasoning, each expert has concluded that the above-identified application contains sufficient disclosure of a method of treating bradycardia using a botulinum toxin to enable one of ordinary skill in the art to practice the invention without undue experimentation.

For example, as stated at paragraph 6 of the November 5, 2001 Longhurst Declaration (hereinafter Longhurst #1), Dr. Longhurst's expert opinion is that "this patent application provides sufficient disclosure and teaching so that a cardiologist of ordinary skill can successfully treat bradycardia by administration of a botulinum toxin into an existing pericardial space of a human patient to thereby increase the heart rate of a patient with symptomatic bradycardia."

Dr. Longhurst further states at paragraph 7 of Longhurst #1 that "matters such as the specific time period in which the toxin should be administered or for how long, and the specific dosage of the botulinum toxin to use entail consideration of factors such as the patient's size, weight, age, and disease severity which factors are routine considerations determined on a patient by patient basis by a cardiologist of ordinary skill who has knowledge of the therapeutic use of a botulinum toxin."

These statements are reiterated in Dr. Longhurst's Declaration dated March 27, 2002 (hereinafter Longhurst #2). In addition, paragraph 2 of Longhurst #2 establishes that Dr. Longhurst's expert opinion is based on several well known scientific facts, which are identified in the above-identified application: "(1) the heart receives sympathetic and parasympathetic innervation (page 1, lines 15-16 of the patent application); (2) sympathetic (adrenergic) stimulation of the heart increases heart rate (page 1, line 16 of the patent application); (3) parasympathetic (cholinergic/vagal) stimulation of the heart decreases heart rate (page 1, lines 17-18 of the patent application); (4) local administration of botulinum toxin causes a reversible inhibition of acetylcholine release from cholinergic nerve terminals (page 13, lines 1-6 of the patent application)." As noted above, this conclusion is based on the disclosure of the above-identified application, taken as a whole.

At paragraph 3 of Longhurst #2, Dr. Longhurst states that "it is reasonable to conclude, as set forth at page 22, lines 18-24 of the patent application, that for a patient with symptomatic bradycardia, vagal nerve inhibition and hence an increase in heart rate can be accomplished by administration of botulinum toxin into an existing pericardial space in the presence of a pericardial effusion of sufficient magnitude to allow access to the pericardial space, to thereby increase the heart rate of a patient with symptomatic bradycardia."

Similarly, a Declaration of Dr. Brin (hereinafter the Brin Declaration) dated February 14, 2003 establishes that Dr. Brin is a well-established expert in the field of botulinum toxin therapy. Based on his review of the above-identified application, Dr. Brin states that the "patent application provides sufficient disclosure and teaching so that a physician of ordinary skill can successfully treat bradycardia by administration of a botulinum toxin into an existing pericardial space of a human patient to thereby increase the heart rate of a patient with symptomatic bradycardia." (paragraph 13 of the Brin Declaration).

Furthermore, at paragraph 14, Dr. Brin states that his conclusion is based on the same well-known facts provided in Longhurst #2, paragraph 2, i.e., "(1) the heart receives sympathetic and parasympathetic innervation (page 1, lines 15-16 of the patent application); (2) sympathetic (adrenergic) stimulation of the heart increases heart rate (page 1, line 16 of the patent application); (3) parasympathetic (cholinergic/vagal) stimulation of the heart decreases heart rate (page 1, lines 17-18 of the patent application); (4) local administration of botulinum toxin causes a reversible inhibition of acetylcholine release from cholinergic nerve terminals (page 13, lines 1-6 of the patent application)."

Dr. Brin further states at paragraph 15 of the Brin Declaration, "it is reasonable to conclude, as set forth at page 22, lines 18-24 of the patent application, that for a patient with bradycardia, vagal nerve inhibition and hence an increase in heart rate can be accomplished by intrapericardial injection of a botulinum toxin to the heart of a patient with bradycardia. Indeed, medical researchers have recently published a study (Masato T., et al., *Botulinum neurotoxin A blocks cholinergic ganglionic neurotransmission in the dog heart*, Jpn J. Pharmacol 2002; 89(3):249-254) wherein it was demonstrated that administration of a botulinum toxin to the sinoatrial node of dog heart blocks

parasympathetic (i.e. cholinergic) mediated bradycardia, and I am in agreement with their conclusion that this foreshadows clinical use of botulinum toxin to treat bradycardia, as set forth in the patent application."

At paragraph 16 of the Brin Declaration, Dr. Brin states that "matters such as the specific time period in which the toxin should be administered or for how long, and the specific dosage of the botulinum toxin to use entail consideration of factors such as the patient's size, weight, age, and disease severity, which factors are routine considerations determined on a patient by patient basis by the treating physician who has knowledge of the therapeutic use of a botulinum toxin."

Thus, because Appellant has provided substantial factual evidence in the form of declarations of highly skilled medical doctors (i.e., experts) in the field of the present invention that supports Appellant's position that the claims are enabled by the instant application, and because the present claims are described and enabled by the specification, as discussed herein, Appellant submits that the rejections under 35 U.S.C. § 112, first paragraph are in error.

In addition, Appellant has submitted post-filing date evidence that corroborates the operability of the claimed invention and mitigates against the alleged contradictory nature of the prior art alleged by the Examiner. This evidence was submitted by way of the publication by Masato T., et al., *Botulinum neurotoxin A blocks cholinergic ganglionic neurotransmission in the dog heart*, Jpn J. Pharmacol 2002; 89(3):249-254, identified in the Brin Declaration. (For the record, Appellant submits that the author's first name is Masato, and the author's last name is Tsuboi. For the purposes of consistency, Appellant will continue to refer to this reference as Masato et al.).

Post-filing date evidence has been permitted by courts to show the effectiveness of compositions for the alleged use despite the

fact that there was no specific examples or test data in the application as originally filed showing the effectiveness of compositions for the claimed use. In re Jolles, 206 USPQ 885 (CCPA 1980).

The Masato et al. reference demonstrates that administration of a botulinum toxin to a region of the heart containing parasympathetic neurons blocks bradycardia mediated by parasympathetic neuronal activity. Although the Examiner has stated that Masato et al. discloses injection of botulinum toxin to the sinoatrial fat pad as opposed to the sinoatrial node, it is important to point out that in the Brin Declaration, Dr. Brin, an expert in the field of the invention, interprets the disclosure of a sinoatrial fat pad injection similar to a sinoatrial node injection.

One important feature established by the Masato et al. reference and the Brin Declaration is that, in the context of the present invention, the botulinum toxin is administered to a single region of the heart with a substantial number of parasympathetic neuronal processes, and that after injecting the botulinum toxin into such a region, the symptoms of bradycardia are treated. Thus, the evidence provided by Masato et al. confirms the operability of the present invention as disclosed in the above-identified application despite the alleged contradictory nature of the prior art asserted by the Examiner.

In view of the above, Appellant submits that the record, as a whole, clearly establishes that the present claims are described in the specification to enable a person of ordinary skill in the art to practice the invention.

With regards to the specific items above, and item 1 in particular, it is well established that working examples are not required in a patent application if the specification contains a sufficient description of the invention so that one skilled in the art will be able to practice the invention without an undue amount

of experimentation. In re Borkowski, 422 F.2d 904, 908, 164 USPQ 642, 645 (CCPA 1970). Compliance with the enablement requirement of 35 U.S.C. § 112, first paragraph, does not turn on whether an example is disclosed (MPEP § 2164.02).

As to items 2 and 3, Appellant submits that specific dosages and administration times are elements of a therapeutic treatment that are routine to persons of ordinary skill in the art, and that such elements do not require undue experimentation. For example, both of the declarants, Dr. Longhurst and Dr. Brin, have stated that such elements are routine to persons of ordinary skill in the art. As understood by persons of ordinary skill in the art, dosages and administration times are optimized depending on the particular patient being treated. Appellant submits that it is not necessary to specify the specific dosage or duration of administration if it is obvious to one skilled in the art that such information could be obtained without undue experimentation. The courts have held that determining proper dosage amounts for an established treatment is routine and could be adjusted to suit the needs of an individua1. U.S. v. Telectronics, Inc. 8 USPQ2d 1217, 1223 (Fed. Cir. 1988). Therefore, Appellant respectfully contends that the specification is enabling because persons of ordinary skill in the art would know how to conduct a dose response study to determine the appropriate amounts to be used and the durations of administration, if necessary.

As to item 4, Appellant submits that disclosing all possible effects mediated by administering botulinum toxin is not required to satisfy 35 U.S.C. § 112. What is required is that the specification disclose the invention (i.e., method of treating bradycardia) so that a person of ordinary skill in the art can practice the invention. Appellant is not attempting to claim the side effects of botulinum toxin therapy. Accordingly, the issue of whether side effects are disclosed is irrelevant to whether the claims are properly described in the specification to satisfy 35

U.S.C. § 112. The applicant need not demonstrate that the invention is completely safe (MPEP § 2164.01(c)).

As to item 5, Appellant submits that the results of the method are not complex and unpredictable when taken in view of the present specification. Botulinum toxin has been successfully used clinically and experimentally to inhibit acetylcholine release from cholinergic neurons. These effects have been used to provide therapeutic treatments for numerous conditions involving undesirable amounts of acetylcholine release from cholinergic neurons. Thus, Appellant submits that it would not be unpredictable to determine that a botulinum toxin would inhibit acetylcholine release from cholinergic parasympathetic neurons, thereby treating bradycardia, which involves the release of acetylcholine from such cholinergic parasympathetic neurons.

As to item 6, Appellant submits that the state of the art is not contradictory. As discussed above, post-filing date evidence in the form of the Masato et al. reference confirms the operability of the present invention as disclosed in the above-identified application. Any alleged contradiction in the prior art can be attributed to differences in experimental paradigms used in those studies, such as the systemic administration. In contrast, the present invention is directed to local administration, i.e., non-systemic administration, of a botulinum toxin to a specific region of a heart (i.e., the SA node or AV node).

In view of the above, Appellant submits that the rejections maintained by the Examiner are in error. In addition, as discussed herein, Appellant submits that the present claims are properly described in the present specification to enable a person of ordinary skill in the art to practice the invention.

B. The present application satisfies the requirements of 35 U.S.C. § 112, first paragraph

The determination that "undue experimentation" would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all factual considerations (see e.g., MPEP §§ 2164.02, 2164.03, 2164.05(a), 2164.05(b), 2164.06, and 2164.08). As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. § 112 is satisfied. In re Fisher , 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. Ex parte Forman, 230 USPQ 546, 547 (BPAI 1986). "The enablement requirement is met if the description enables any mode of making and using the claimed invention." Engel Indus., Inc. v. Lockformer Co., 946 F.2d 1528, 1533 (Fed.Cir.1991).

The above-identified application discloses the use of a neurotoxin in general, and botulinum toxin in particular, in the claimed methods. Examples are provided regarding the use of botulinum toxin type A. The specification as a whole provides sufficient guidance regarding the use of botulinum toxin to treat bradycardia so that any additional experimentation needed to practice the claimed invention would simply be routine to a person of ordinary skill in the art. For example, the specification discloses dosage ranges that are appropriate in treating bradycardia. As indicated by the declarants, Dr. Longhurst and Dr. Brin, determination of specific dosages and administration

schedules are normally determined based on a patient's particular medical condition, and thus, such determinations are routine to those of ordinary skill in the art. The specification discloses that the administration of a botulinum toxin to cardiac tissue, such as the SA node or AV node, where parasympathetic ganglion neurons are plentiful, alleviates the symptoms of bradycardia (i.e., alleviates the reduction in heart rate).

In view of the above, Appellant submits that the present specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim.

1. The specification describes the subject matter defined by each of the rejected claims

Claim 7 recites a method for treating bradycardia. The method comprises the step of intrapericardial injection of a botulinum toxin to the sinoatrial node or to the atrioventricular node of a heart of a patient with bradycardia, thereby treating bradycardia.

The present specification discloses generally at page 20, lines 9-13 administration of a neurotoxin in the vicinity of a parasympathetic neuron, and at page 23, lines 12-17, and page 24, lines 14-18 intrapericardial injection in the vicinity of the SA node to reduce bradycardia symptoms for about two to four months, and by example at page 31, lines 6-17; and page 33, lines 8-10 intrapericardial injection adjacent to the SA node or the AV node to provide treatment of bradycardia.

Claims 15-17 are dependent from claim 7 and recite dosages of a botulinum toxin type A that are used to treat bradycardia.

The present specification discloses at page 21, lines 2-10; page 29, lines 24-26; page 25, lines 7-28; page 32, lines 3-5; page 32, line 20; page 33, lines 4-8; and page 33, lines 18-21 suitable dosages of botulinum toxin type A

Claim 37 is dependent from claim 7 and limits claim 1 by indicating that the botulinum toxin is selected from the group consisting of botulinum toxin types A, B, C, D, E, F and G.

Claim 37 is described in specification at page 22, lines 1-3; and page 34, lines 14-16.

Claim 38 is an independent claim directed to the treatment bradycardia by administering a botulinum toxin type A to the sinoatrial node or to the atrioventricular node of a heart of a patient with bradycardia.

The present specification describes the use of botulinum toxin type A to treat bradycardia generally at page 20, lines 6-13; page 21, lines 4-10; page 22, lines 5-16; page 23, lines 11-17; page 25, lines 23-29; page 29, lines 24-26; and specifically at page 31, lines 6-17.

Thus, Appellant submits that the subject matter recited in the present claims is sufficiently described in the present specification to satisfy the requirements of 35 U.S.C. § 112.

2. The specification contains a description to enable a person of ordinary skill in the art to practice the invention defined by each of the rejected claims without undue experimentation

The determination of undue experimentation in connection with the treatment of patients with bradycardia by administering a botulinum toxin to the patient involve a balancing of the factors enumerated in Ex Parte Forman 230 U.S.P.Q. 546 (BPAI 1986). These factors include:

a) the quantity of experimentation necessary;
b) the amount of guidance presented;
c) the presence or absence of working examples;
d) the nature of the invention;
e) the state of the prior art;

f) the relative skill of those in the art;

g) the predictability or unpredictability of the art; and

h) the breadth of the claims.

The Forman Factors Are Met By Appellant's Disclosure:

A. THE QUANTITY OF EXPERIMENTATION NECESSARY

Appellant submits that the quantity of experimentation that may be necessary to practice the invention is minimal and is not undue in view of Appellant's disclosure in the instant application. Moreover, any such experimentation is routine (see Longhurst #1 and #2, and the Brin Declaration).

The claimed invention recites a step of intrapericardial injection of a botulinum toxin to an SA node or AV node of a patient's heart to treat bradycardia. In view of the present specification, the step of administering a therapeutic agent to cardiac tissue is routine. For example, the specification has incorporated by reference several prior art references, such as *Harrison's Principles of Internal Medicine* (1997), edited by Anthony Fauci et al., 14th edition, published by McGraw Hill); Circulation, 85(4); 1582-1593 (1992); Am Heart J., 1996 Nov; 132(5): 969-972; Cath & Cardiovasc Diagn 1997 Nove; 42(3):313-20; Int J Artificial Organs 1997 Jun; 20(6): 319-26; J Cardio Pharm 24: 826-40 (1994); and Cath & Cardiovasc Interv 1999; May; 47(1): 109-11, to support the fact that such steps are well-known and practiced in the art at the time of the invention. In addition, the Examiner has acknowledged that the step of administration is routine. (see October 18, 2002 Office Action, page 8-9).

In addition, the use of a botulinum toxin as a therapeutic agent is routine for persons of ordinary skill in the art. As explained in the July 24, 2002 Response, Appellant has identified numerous therapeutic uses of botulinum toxin to treat conditions involving acetylcholine release from cholinergic neurons (e.g., see

pages 11-12 of the July 24, 2002 response). Based on the foregoing, it is reasonable to conclude based on the state of the prior art that botulinum toxin would inhibit acetylcholine release from cholinergic neurons in cardiac tissue since it was known that botulinum toxin inhibits acetylcholine release from other cholinergic neurons. Any differences in dosage or administration schedule among various treatments would be determined on a case by case basis by the attending physician, and is routine to persons of ordinary skill in the art (e.g., see Longhurst #1 and #2, and Brin Declaration).

B. THE AMOUNT OF DIRECTION OR GUIDANCE PRESENTED

The present specification discloses multiple methods in which a botulinum toxin may be administered to a patient. The claimed invention is directed to a method including intrapericardial injection. The disclosure of the specification in general, and the examples of the specification in particular, teach several methods for accessing cardiac tissue, and for intrapericardially injecting a botulinum toxin into a patient. In addition, the specification discloses that the therapeutic effects are noted by an increase in heart rate, and persist for two to four months.

In addition, the specification discloses what bradycardia is and how the neurological systems of a patient may influence bradycardia. For example, bradycardia can be defined as any disturbance of the heart's rhythm which results in a heart rate of under sixty beats per minute (page 7, lines 9-11). The pumping action of the heart is controlled by sympathetic and parasympathetic nerves (page 1, lines 15-16). The parasympathetic nerves that innervate the heart are cholinergic nerves that release acetylcholine as a neurotransmitter (page 1, lines 21-22). The release of acetylcholine by the parasympathetic nerves results in a decrease of the rhythm rate of the SA node through the activation of cholinergic muscarinic receptors present in cardiac muscle

tissue (page 1, lines 25-30). The release of acetylcholine also decreases the excitability of AV junctional fibers between the atrial musculature and the AV node to slow transmission of the cardiac impulse into the ventricles (page 1, lines 25-30).

The specification discloses that administration of botulinum toxin intrapericardially in the vicinity of the SA node results in an increase in heart rate by inhibiting the vagal nerve of the heart (page 23, lines 11-13). The SA and AV nodes contain a high proportion of cholinergic parasympathetic nerves, and thus, administration of a botulinum toxin to the SA and AV nodes results in inhibition of acetylcholine release from these cholinergic parasympathetic nerves (page 24, lines 7-18).

Thus, the present specification clearly discloses that bradycardia is a condition that involves acetylcholine release from parasympathetic nerves and that inhibition of the release of acetylcholine from the parasympathetic nerves, such as the parasympathetic nerves of the SA and/or AV nodes of a heart, can attenuate the reduction in the heart rate of a patient with bradycardia.

The specification also discloses how a botulinum toxin is administered to a patient to enable one of ordinary skill in the art to administer a botulinum toxin without undue experimentation.

As acknowledged in the specification, the method for determining the appropriate route of administration is generally determined on a case by case basis by the attending physician. In other words, physicians performing cardiac procedures are intimately familiar with various techniques for delivering a therapeutic agent to cardiac tissue that can be chosen depending on the patient (page 24, line 28 to page 25, line 2). More specifically, the specification discloses that a botulinum toxin is administered intrapericardially to facilitate contact of the toxin with the postganglionic parasympathetic nerve endings (page 25, lines 3-5). The specification discloses accessing the pericardial

space through the right atrial appendage (page 25, lines 4-6) and by catheterization using a needle tip and a catheter, such as an infusion sleeve catheter or microporous balloon catheter (page 25, line 15-19), among others. In addition, controlled release implants containing the botulinum toxin may be placed in direct contact with the pericardium (page 27, lines 5-6). To further support the disclosure that the methods of accessing the pericardium for therapeutic purposes are well known and routine to persons of ordinary skill in the art at the time of the invention, the specification has incorporated by reference several references, such as *Harrison's Principles of Internal Medicine* (1997), edited by Anthony Fauci et al., 14th edition, published by McGraw Hill); Circulation, 85(4); 1582-1593 (1992); Am Heart J., 1996 Nov; 132(5): 969-972; Cath & Cardiovasc Diagn 1997 Nove; 42(3):313-20; Int J Artificial Organs 1997 Jun; 20(6): 319-26; J Cardio Pharm 24: 826-40 (1994); and Cath & Cardiovasc Interv 1999; May; 47(1): 109-11.

The above-identified application discloses that the phrase "botulinum toxin" currently includes seven known types which commonly inhibit acetylcholine release from cholinergic neurons (page 12, lines 23-26 and page 13, lines 11-25, and page 17, lines 6-8). One type of purified botulinum toxin type A is commercially and publicly available under the trade name Botox® by Allergan, Irvine, CA, and under the trade name Dysport from Porton Products Ltd., U.K. (page 16, lines 9-12).

In addition, the above-identified application discloses two specific examples in which the methods can be practiced.

For example, Example 1 discloses a method of treating a patient by administering Botox® to cardiac tissue. In particular, example 1 states that a right ventricular injection can be made by introducing a catheter with a retractable sheathed needle via the right internal jugular vein using the usual Seldinger technique. The catheter is advanced to the lateral wall of the right atrium

under fluoroscopic guidance. The catheter is then advanced toward the interventricular septum, which is confirmed using oblique fluoroscopic projections or two dimensional endocardiography methods. Contact with the myocardium is confirmed by the presence of premature ventricular contractions, lack of further advancement, and transmission of ventricular impulse to the operator. The needle in the catheter is then exposed and advanced into the myocardium. The Botox® is then injected into the myocardium, and the catheter is withdrawn. Example 1 also discloses a method of injecting Botox® into cardiac tissue by way of a catheter that is advanced through a femoral artery in the groin of a patient, with methods of determining that the catheters are properly placed in the desired cardiac regions. Botox® is injected, and the bradycardia symptoms are reduced within about seven days, and remain alleviated for two to four months after the injection.

Example 2 discloses a specific method of intrapericardially injecting Botox® into a patient. As indicated, a needle tip is inserted through an unopened chest wall, and guided by fluoroscopy, through the pericardium. Botox® is injected adjacent to the SA node or AV node in the vicinity where the vagal nerves terminate on the heart. In particular, the toxin is administered at a location within the pericardium, under the endocardium, between the SA and AV nodes.

In summary, Appellant submits that the present specification contains sufficient disclosure to enable one of ordinary skill in the art to practice the invention. In addition, the claimed methods recite a standard modes of administration of a therapeutic agent (i.e., a botulinum toxin) to a patient. Appellant submits that at the time of filing the above-identified application, persons of ordinary skill in the art recognized the disclosed modes of administration as standard, and accordingly, 35 U.S.C. § 112, first paragraph is satisfied with respect to the step of administering a botulinum toxin to a patient. This fact has been

confirmed by two experts in the field of the invention by way of the declarations discussed above.

With respect to the lack of a disclosure on specific dosages of botulinum toxin, Appellant submits that parameters such as dosages and timing and methods of administration of therapeutic agents may need to be optimized for clinical trials and ultimate commercial application is not the proper standard for disclosure under 35 U.S.C. § 112.

As discussed above, optimizing the dosage of a particular therapeutic agent is considered routine to persons of ordinary skill in the art. For example, it is routine to perform dose response studies to determine the appropriate dosage of a therapeutic agent to treat a patient. U.S. v. Telectronics, Inc. 8 USPQ2d 1217, 1223 (Fed. Cir. 1988). In addition, two experts (Dr. Longhurst and Dr. Brin) have declared that dosages and administration schedules are routine and typically determined for a patient on a case by case basis.

Therefore, Appellant respectfully submits that the present specification is enabling because persons of ordinary skill in the art would know how to conduct a dose response study and other procedures to determine the appropriate amounts of botulinum toxin to be used. This is especially true given that the present specification contains suitable ranges of dosages of botulinum toxin.

Appellant respectfully contends that the law as set forth in In re Wands (In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988)) and in numerous other cases, provides that "[e]nablement is not precluded by the necessity of some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation, the key word is 'undue' not 'experimentation.'" In re Angstadt, 190 USPQ 214 (C.C.P.A. 214), the court stated, in reference to broad claims supported by working examples of more limited scope, that a requirement to perform all

the possible experiments to support the scope of the claims "would force an inventor seeking adequate patent production to carry out a prohibitive number of actual experiments. This would tend to discourage inventors from filing applications in an unpredictable area since the patent claims would have to be limited to those embodiments which are expressly disclosed. A potential infringer could readily avoid 'literal' infringement of such claims by merely finding another analogous catalyst complex which could be used in forming peroxides." The court concluded that the "experimentation required to determine which catalysts will produce hydroperoxides would not be undue and certainly would not 'require ingenuity beyond that to be expected by one of ordinary skill in the art'."

Although the specific examples in the present specification are directed to the use of botulinum toxin type A, Appellant submits that substitution of one type of botulinum toxin for another type of botulinum toxin to treat bradycardia, which involves an increase in acetylcholine release from the cholinergic parasympathetic neurons, would not require undue experimentation since each of the different types of botulinum toxins are known to inhibit acetylcholine release, which inhibition is disclosed in the present specification as being important with respect to the present invention. Any additional experimentation regarding determination of the dosages or administration timing would be routine, as discussed above.

In the present case, Appellant has disclosed how to access cardiac tissue to deliver a therapeutic agent, how to administer a botulinum toxin to a patient, how much botulinum toxin to administer, and the therapeutic effects obtained by administering botulinum toxin to a patient. Following the instructions provided by Appellant in the above-identified application, it is a simple and routine matter for one of ordinary skill in the art to administer a botulinum toxin to treat bradycardia, as claimed.

C. THE PRESENCE OR ABSENCE OF WORKING EXAMPLES

As discussed above, in determining whether claims are supported by a specification under 35 U.S.C. § 112, first paragraph, all of the evidence of record must be used in making the determination. Working examples are not required. Appellant submits that the present application taken as a whole provides ample guidance to enable a person of ordinary skill in the art to practice the invention without undue experimentation. This submission is confirmed by two experts in the field of the invention (i.e., Dr. Longhurst and Dr. Brin), as discussed above.

D. THE NATURE OF THE INVENTION

The invention relates to a method of treating bradycardia by intrapericardially injecting a botulinum toxin into a SA node or AV node of a heart of a patient with bradycardia. The botulinum toxin inhibits release of acetylcholine from cholinergic neurons, thereby resulting in a reduction of bradycardia symptoms. The claimed invention is not complex or unpredictable as asserted by the Examiner. The invention utilizes well-known administration techniques, and a therapeutic agent that is known to inhibit acetylcholine release. The administration of botulinum toxin inhibits acetylcholine release to attenuate the reduction in heart rate associated with bradycardia. Treatment is readily determined by monitoring the heart rate of the patient.

E. THE STATE OF THE PRIOR ART

Information about the state of the art that is relevant to the analysis of whether undue experimentation would have been required concerns whether those skilled in the art would be sufficiently familiar with the methods needed to practice the invention. As discussed herein, and as acknowledged by the Examiner, the step of administering a therapeutic agent to cardiac tissue is well known in the art at the time of the invention. In addition, the prior

art has clearly established that acetylcholine release from cholinergic neurons is inhibited by botulinum toxin.

The only uncertainty presented in the art as identified by the Examiner is whether botulinum toxin provides a therapeutic effect in the treatment of bradycardia. The differences presented in the prior art references relied upon by the Examiner may be attributed to the different experimental paradigms used in those references. For example, the prior art references, such as Lamanna et al., disclose systemic administration of a botulinum toxin, which is in contrast to the present invention which recites intrapericardial injection (i.e., non-systemic administration).

However, as discussed above, since the filing date of the instant application, scientists have reported that botulinum toxin locally administered to the cholinergic parasympathetic neurons of the heart successfully alleviates bradycardia-like symptoms associated with cholinergic neuronal activity (Masato et al. discussed above). Indeed, this has been supported by the Dr. Brin's Declaration discussed above.

Although the Examiner has indicated that administration of a botulinum toxin to the SA fat pad is different than administration of a botulinum toxin to the SA node, it is important to note that both regions contain a high proportion of cholinergic parasympathetic neurons. Accordingly, the operability of the claimed invention is confirmed by the disclosure of Masato et al. relating to the administration of a botulinum toxin to the cholinergic parasympathetic neurons of the heart. Furthermore, despite the Examiner's opinion that the disclosure of Masato et al. is contradictory, it is important to note that Masato and the other authors conclude that local administration of botulinum toxin blocks bradycardia mediated by parasympathetic ganglionic activation (see Abstract, last sentence). Thus, despite the alleged contradictory nature of the prior art, Appellant submits that the present invention operates as claimed.

F. THE RELATIVE SKILL OF THOSE IN THE ART

There was a high level of skill in the art at the time of Appellant's invention. Physicians having medical degrees as well as substantial clinical and possible research experience are the norm. The method steps recited in the present claims are well known to those persons of ordinary skill in the art.

G. THE PREDICTABILITY OR UNPREDICTABILITY OF THE ART

While there will always be some unpredictability in introducing an agent into the human body, the amount of unpredictability is considerably lessened when a known technique and a known agent are used for the treatment. As discussed above, Appellant submits that the unpredictability associated with the targeted administration of a botulinum toxin to the SA node or AV node is minimal since both the administration techniques and the physiological effects of botulinum toxin were known at the time of the invention.

H. THE BREADTH OF THE CLAIMS

Appellant's claims are narrowly tailored to methods for treating bradycardia by intrapericardially injecting a specific class of neurotoxins, i.e., a botulinum toxin, into specific regions of the heart with a relatively dense population of cholinergic neurons, i.e., the SA node or AV node. Since the claims are directed to a specific class of neurotoxins that have a common effect on a common population of neurons, and to a specific target site to achieve a therapeutic effect, Appellant submits that the present claims are not unduly broad, and are properly supported by the specification under 35 U.S.C. § 112.

IX. CONCLUSION

In view of the above, Appellant submits that the standards for enablement under 35 U.S.C. § 112, first paragraph, have been met. As discussed herein, the claimed methods recite conventional modes of administration of a well-characterized neurotoxin, i.e., botulinum toxin, to a patient. This fact has been confirmed by two experts in the field of the invention by way of the declarations discussed above. Thus, undue experimentation is not required to practice the claimed invention, nor is there a lack of predictability of success for the claimed method. In view of Appellant's teaching in the above-identified specification and the prior art, the present disclosure meets the enablement requirement of 35 U.S.C. § 112 and withdrawal of the 35 U.S.C. § 112 rejection is respectfully expected. Therefore, Appellant respectfully requests this Honorable Board to reverse the Examiner's rejection and hold claims 7, 15-17, and 37-38 allowable.

Respectfully submitted,

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APPENDIX A

CLAIMS ON APPEAL

7. A method for treating bradycardia, the method comprising the step of intrapericardial injection of a botulinum toxin to the sinoatrial node or to the atrioventricular node of a heart of a patient with bradycardia, thereby treating bradycardia.

15. The method of claim 7, wherein the botulinum toxin is botulinum toxin type A and the amount of botulinum toxin type A locally administered to the heart is between about 0.01 U/kg and about 35 U/kg.

16. The method of claim 7 wherein the botulinum toxin is botulinum toxin type A and the amount of botulinum toxin type A locally administered to the heart is between about 0.1 U/kg and about 30 U/kg.

17. The method of claim 7, wherein the botulinum toxin is botulinum toxin A and the amount of botulinum toxin A locally administered to the heart is between about 1 U/kg and about 25 U/kg.

37. The method of claim 7, wherein the botulinum toxin is selected from the group consisting of botulinum toxin types A, B, C, D, E, F and G.

38. A method for treating bradycardia, the method comprising the step of intrapericardial injection of a botulinum toxin type A to the sinoatrial node or to the atrioventricular node of a heart of a patient with bradycardia, thereby treating bradycardia.